ZERIT â (stavudine)

Rx only

ZERIT® (stavudine) Capsules

ZERIT® (stavudine) for Oral Solution

(Patient Information Leaflet Included)

WARNING

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING STAVUDINE AND OTHER ANTIRETROVIRALS. FATAL LACTIC ACIDOSIS HAS BEEN REPORTED IN PREGNANT WOMEN WHO RECEIVED THE COMBINATION OF STAVUDINE AND DIDANOSINE WITH OTHER ANTIRETROVIRAL AGENTS. THE COMBINATION OF STAVUDINE AND DIDANOSINE SHOULD BE USED WITH CAUTION DURING PREGNANCY AND IS RECOMMENDED ONLY IF THE POTENTIAL BENEFIT CLEARLY OUTWEIGHS THE POTENTIAL RISK (SEE WARNINGS AND PRECAUTIONS: PREGNANCY).

FATAL AND NONFATAL PANCREATITIS HAVE OCCURRED DURING THERAPY WHEN ZERIT WAS PART OF A COMBINATION REGIMEN THAT INCLUDED DIDANOSINE, WITH OR WITHOUT HYDROXYUREA, IN BOTH TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION (SEE WARNINGS).

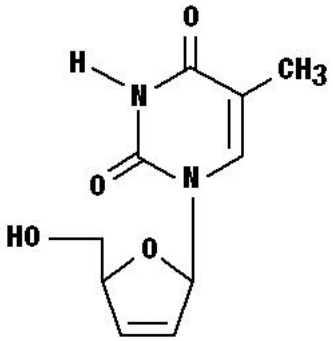
DESCRIPTION

ZERIT® is the brand name for stavudine (d4T), a synthetic thymidine nucleoside analogue, active against the Human Immunodeficiency Virus (HIV).

ZERIT (stavudine) Capsules are supplied for oral administration in strengths of 15, 20, 30, and 40 mg of stavudine. Each capsule also contains inactive ingredients microcrystalline cellulose, sodium starch glycolate, lactose, and magnesium stearate. The hard gelatin shell consists of gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and iron oxides.

ZERIT (stavudine) for Oral Solution is supplied as a dye-free, fruit-flavored powder in bottles with child-resistant closures providing 200 mL of a 1 mg/mL stavudine solution upon constitution with water per label instructions. The powder for oral solution contains the following inactive ingredients: methylparaben, propylparaben, sodium carboxymethylcellulose, sucrose, and antifoaming and flavoring agents.

The chemical name for stavudine is 2',3'-didehydro-3'-deoxythymidine. Stavudine has the following structural formula:



Stavudine is a white to off-white crystalline solid with the molecular formula $C_{10}H_{12}N_2O_4$ and a molecular weight of 224.2. The solubility of stavudine at 23° C is approximately 83 mg/mL in water and 30 mg/mL in propylene glycol. The n-octanol/water partition coefficient of stavudine at 23° C is 0.144.

MICROBIOLOGY

Mechanism of Action

Stavudine, a nucleoside analogue of thymidine, inhibits the replication of HIV in human cells *in vitro*. Stavudine is phosphorylated by cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV reverse transcriptase both by competing with the natural substrate deoxythymidine triphosphate (K_i = 0.0083 to 0.032 μM), and by its incorporation into viral DNA causing a termination of DNA chain elongation because stavudine lacks the essential 3'-OH group. Stavudine triphosphate inhibits cellular DNA polymerase beta and gamma, and markedly reduces the synthesis of mitochondrial DNA.

In vitro HIV Susceptibility

The *in vitro* antiviral activity of stavudine was measured in peripheral blood mononuclear cells, monocytic cells, and lymphoblastoid cell lines. The concentration of drug necessary to inhibit viral replication by 50% (ED_{50}) ranged from 0.009 to 4 μM against laboratory and clinical isolates of HIV-1. Stavudine had additive and synergistic activity in combination with didanosine and zalcitabine, respectively, *in vitro*. Stavudine combined with zidovudine had additive or antagonistic activity *in vitro* depending upon the molar ratios of the agents tested. The relationship between *in vitro* susceptibility of HIV to stavudine and the inhibition of HIV replication in humans has not been established.

Drug Resistance

HIV isolates with reduced susceptibility to stavudine have been selected *in vitro* and were also obtained from patients treated with stavudine. Phenotypic analysis of HIV isolates from stavudine-treated patients revealed, in 3 of 20 paired isolates, a 4- to 12-fold decrease in susceptibility to stavudine *in vitro*. The genetic basis for these susceptibility changes has not been identified. The clinical relevance of changes in stavudine susceptibility has not been established.

Cross-resistance

Five of 11 stavudine post-treatment isolates developed moderate resistance to zidovudine (9- to 176-fold) and 3 of those 11 isolates developed moderate resistance to didanosine (7- to 29-fold). The clinical relevance of these findings is unknown.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults

The pharmacokinetics of stavudine have been evaluated in HIV-infected adult and pediatric patients (Table 1). Peak plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) increased in proportion to dose after both single and multiple doses ranging from 0.03 to 4 mg/kg. There was no significant accumulation of stavudine with repeated administration every 6, 8, or 12 hours.

Absorption

Following oral administration, stavudine is rapidly absorbed, with peak plasma concentrations occurring within 1 hour after dosing. The systemic exposure to stavudine is the same following administration as capsules or solution.

Distribution

Binding of stavudine to serum proteins was negligible over the concentration range of 0.01 to 11.4 μg/mL. Stavudine distributes equally between red blood cells and plasma.

Metabolism

The metabolic fate of stavudine has not been elucidated in humans.

Excretion

Renal elimination accounted for about 40% of the overall clearance regardless of the route of administration. The mean renal clearance was about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration.

Table 1:	**Mean ± SD Pharmacokinetic Parameters of Stavudine in Adult and Pediatric HIV-Infected Patients**			
Parameter	Adult Patients	n	Pediatric Patients	n
Oral bioavailability (F)	86.4 ± 18.2%	25	76.9 ± 31.7%	20
Volume of distribution[a] (VD)	58 ± 21 L	44	18.5 ± 9.2 L/m^2	21
Apparent oral volume of distribution[b] (VD/F)	66 ± 22 L	71	not determined	-
Ratio of CSF: plasma concentrations (as %)[c]	not determined	-	59 ± 35%	8
Total body clearance[a] (CL)	8.3 ± 2.3 mL/min/kg	44	247 ± 94 mL/min/m^2	21
Apparent oral clearance[b] (CL/F)	8.0 ± 2.6 mL/min/kg	113	333 ± 87 mL/min/m^2	20
Elimination half-life ($T_{½}$), IV dose[a]	1.15 ± 0.35 h	44	1.11 ± 0.28 h	21
Elimination half-life ($T_{½}$), oral dose[b]	1.44 ± 0.30 h	115	0.96 ± 0.26 h	20
Urinary recovery of stavudine (% of dose)	39 ± 23%	88	34 ± 16%	19
[a] following 1 hour IV infusion [b] following single oral dose [c] following multiple oral doses				

Special Populations

Pediatric

For pharmacokinetic properties of stavudine in pediatric patients see Table 1.

Renal Insufficiency

Data from two studies indicated that the apparent oral clearance of stavudine decreased and the terminal elimination half-life increased as creatinine clearance decreased (see Table 2). C_{max} and T_{max} were not significantly altered by renal insufficiency. The mean ± SD hemodialysis clearance value of stavudine was 120 ± 18 mL/min (n=12); the mean ± SD percentage of the stavudine dose recovered in the dialysate, timed to occur between 2-6 hours post-dose, was 31 ± 5%. Based on these observations, it is

recommended that ZERIT (stavudine) dosage be modified in patients with reduced creatinine clearance and in patients receiving maintenance hemodialysis (see **DOSAGE AND ADMINISTRATION**).

Table 2: Mean ± SD Pharmacokinetic Parameter Values Single 40-mg Oral Dose of ZERIT

	Creatinine Clearance			Hemodialysis
	>50 mL/min (n=10)	26-50 mL/min (n=5)	9-25 mL/min (n=5)	Patients* (n=11)
CL_{cr} (mL/min)	104 ± 28	41 ± 5	17 ± 3	NA
CL/F (mL/min)	335 ± 57	191 ± 39	116 ± 25	105 ± 17
CL_R (mL/min)	167 ± 65	73 ± 18	17 ± 3	NA
$T_{½}$ (h)	1.7 ± 0.4	3.5 ± 2.5	4.6 ± 0.9	5.4 ± 1.4

CL_{cr} = creatinine clearance
CL/F = apparent oral clearance
CL_R = renal clearance
$T_{½}$ = terminal elimination half-life
NA = not applicable
* Determined while patients were off dialysis.

Hepatic Insufficiency

Stavudine pharmacokinetics were not altered in 5 non-HIV-infected patients with hepatic impairment secondary to cirrhosis (Child-Pugh classification B or C) following the administration of a single 40-mg dose.

Geriatric

Stavudine pharmacokinetics have not been studied in patients >65 years of age. (See **PRECAUTIONS: Geriatric Use**.)

Gender

A population pharmacokinetic analysis of stavudine concentrations collected during a controlled clinical study in HIV-infected patients showed no clinically important differences between males (n=291) and females (n=27).

Race

A population pharmacokinetic analysis of stavudine concentrations collected during a controlled clinical study in HIV-infected patients (233 Caucasian, 39 African American, 41 Hispanic, 1 Asian, and 4 Other) showed no clinically important differences associated with race.

Drug Interactions

Drug interaction studies have demonstrated that there are no clinically significant interactions between stavudine and the following: didanosine, lamivudine, or nelfinavir.

Zidovudine may competitively inhibit the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with ZERIT is not recommended.

INDICATIONS AND USAGE

ZERIT (stavudine), in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection (see Clinical Studies).

Clinical Studies

Combination Therapy

The combination use of ZERIT is based on the results of clinical studies in HIV-infected patients in double- and triple-combination regimens with other antiretroviral agents.

One of these studies (START 1) was a multicenter, randomized, open-label study comparing ZERIT (40 mg twice daily) plus lamivudine plus indinavir to zidovudine plus lamivudine plus indinavir in 202 treatment-naive patients. Both regimens resulted in a similar magnitude of inhibition of HIV RNA levels and increases in CD4 cell counts through 48 weeks.

Monotherapy

The efficacy of ZERIT was demonstrated in a randomized, double-blind study (AI455-019, conducted 1992-1994) comparing ZERIT with zidovudine in 822 patients

with a spectrum of HIV-related symptoms. The outcome in terms of progression of HIV disease and death was similar for both drugs.

CONTRAINDICATIONS

ZERIT is contraindicated in patients with clinically significant hypersensitivity to stavudine or to any of the components contained in the formulation.

WARNINGS

1. Lactic Acidosis/Severe Hepatomegaly with Steatosis/Hepatic Failure:

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including stavudine and other antiretrovirals. Although relative rates of lactic acidosis have not been assessed in prospective well-controlled trials, longitudinal cohort and retrospective studies suggest that this infrequent event may be more often associated with antiretroviral combinations containing stavudine. Female gender, obesity, and prolonged nucleoside exposure may be risk factors. Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk (see **PRECAUTIONS**: **Pregnancy**).

Particular caution should be exercised when administering ZERIT to any patient with known risk factors for liver disease; however, cases of lactic acidosis have also been reported in patients with no known risk factors. Generalized fatigue, digestive symptoms (nausea, vomiting, abdominal pain, and sudden unexplained weight loss); respiratory symptoms (tachypnea and dyspnea); or neurologic symptoms (including motor weakness, see **2. Neurologic Symptoms**) might be indicative of lactic acidosis development.

Treatment with ZERIT should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

An increased risk of hepatotoxicity may occur in patients treated with ZERIT in combination with didanosine and hydroxyurea compared to when ZERIT is used alone. Deaths attributed to hepatotoxicity have occurred in patients receiving this combination. Patients treated with this combination should be closely monitored for signs of liver toxicity.

2. Neurologic Symptoms:

Motor weakness has been reported rarely in patients receiving combination antiretroviral therapy including ZERIT. Most of these cases occurred in the setting of lactic acidosis. The evolution of motor weakness may mimic the clinical presentation of Guillain-Barré syndrome (including respiratory failure). Symptoms may continue or worsen following discontinuation of therapy.

Peripheral neuropathy, manifested by numbness, tingling, or pain in the hands or feet, has been reported in patients receiving ZERIT therapy. Peripheral neuropathy has occurred more frequently in patients with advanced HIV disease, a history of neuropathy, or concurrent neurotoxic drug therapy, including didanosine (see **ADVERSE REACTIONS**).

3. Pancreatitis:

Fatal and nonfatal pancreatitis have occurred during therapy when ZERIT was part of a combination regimen that included didanosine, with or without hydroxyurea, in both treatment-naive and treatment-experienced patients, regardless of degree of immunosuppression. The combination of ZERIT and didanosine (with or without hydroxyurea) and any other agents that are toxic to the pancreas should be suspended in patients with suspected pancreatitis. Reinstitution of ZERIT after a confirmed diagnosis of pancreatitis should be undertaken with particular caution and close patient monitoring. The new regimen should contain neither didanosine nor hydroxyurea.

PRECAUTIONS

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and

"cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Information for Patients (See Patient Information Leaflet.)

Patients should be informed of the importance of early recognition of symptoms of lactic acidosis, which include abdominal discomfort, nausea, vomiting, fatigue, dyspnea, and motor weakness. Patients in whom these symptoms develop should seek medical attention immediately. Discontinuation of ZERIT therapy may be required.

Patients should be informed that an important toxicity of ZERIT (stavudine) is peripheral neuropathy. Patients should be aware that peripheral neuropathy is manifested by numbness, tingling, or pain in hands or feet, and that these symptoms should be reported to their physicians. Patients should be counseled that peripheral neuropathy occurs with greatest frequency in patients who have advanced HIV disease or a history of peripheral neuropathy, and that dose modification and/or discontinuation of ZERIT may be required if toxicity develops.

Caregivers of young children receiving ZERIT therapy should be instructed regarding detection and reporting of peripheral neuropathy.

Patients should be informed that when ZERIT is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when ZERIT is used alone. An increased risk of pancreatitis, which may be fatal, may occur in patients treated with the combination of ZERIT and didanosine, with or without hydroxyurea. Patients treated with this combination should be closely monitored for symptoms of pancreatitis. An increased risk of hepatotoxicity, which may be fatal, may occur in patients treated with ZERIT in combination with didanosine and hydroxyurea. Patients treated with this combination should be closely monitored for signs of liver toxicity.

Patients should be informed that ZERIT (stavudine) is not a cure for HIV infection, and that they may continue to acquire illnesses associated with HIV infection, including opportunistic infections. Patients should be advised to remain under the care of a physician when using ZERIT. They should be advised that ZERIT therapy has not been shown to reduce the risk of transmission of HIV to others through sexual contact or

blood contamination. Patients should be informed that the long-term effects of ZERIT are unknown at this time.

Patients should be informed that the Centers for Disease Control and Prevention (CDC) recommend that HIV-infected mothers not nurse newborn infants to reduce the risk of postnatal transmission of HIV infection.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

Drug Interactions

Zidovudine may competitively inhibit the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with ZERIT (stavudine) is not recommended (see **CLINICAL PHARMACOLOGY**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In 2-year carcinogenicity studies in mice and rats, stavudine was noncarcinogenic at doses which produced exposures (AUC) 39 and 168 times, respectively, human exposure at the recommended clinical dose. Benign and malignant liver tumors in mice and rats and malignant urinary bladder tumors in male rats occurred at levels of exposure 250 (mice) and 732 (rats) times human exposure at the recommended clinical dose.

Stavudine was not mutagenic in the Ames, *E. coli* reverse mutation, or the CHO/HGPRT mammalian cell forward gene mutation assays, with and without metabolic activation. Stavudine produced positive results in the *in vitro* human lymphocyte clastogenesis and mouse fibroblast assays, and in the *in vivo* mouse micronucleus test. In the *in vitro* assays, stavudine elevated the frequency of chromosome aberrations in human lymphocytes (concentrations of 25 to 250 μg/mL, without metabolic activation) and increased the frequency of transformed foci in mouse fibroblast cells (concentrations of 25 to 2500 μg/mL, with and without metabolic activation). In the *in vivo* micronucleus assay, stavudine was clastogenic in bone marrow cells following oral stavudine administration to mice at dosages of 600 to 2000 mg/kg/day for 3 days.

No evidence of impaired fertility was seen in rats with exposures (based on C_{max}) up to 216 times that observed following a clinical dosage of 1 mg/kg/day.

Pregnancy

Pregnancy Category C. Reproduction studies have been performed in rats and rabbits with exposures (based on C_{max}) up to 399 and 183 times, respectively, of that seen at a clinical dosage of 1 mg/kg/day and have revealed no evidence of teratogenicity. The incidence in fetuses of a common skeletal variation, unossified or incomplete ossification of sternebra, was increased in rats at 399 times human exposure, while no effect was observed at 216 times human exposure. A slight post-implantation loss was noted at 216 times the human exposure with no effect noted at approximately 135 times the human exposure. An increase in early rat neonatal mortality (birth to 4 days of age) occurred at 399 times the human exposure, while survival of neonates was unaffected at approximately 135 times the human exposure. A study in rats showed that stavudine is transferred to the fetus through the placenta. The concentration in fetal tissue was approximately one-half the concentration in maternal plasma. Animal reproduction studies are not always predictive of human response.

There are no adequate and well-controlled studies of stavudine in pregnant women. Stavudine should be used during pregnancy only if the potential benefit justifies the potential risk.

Fatal lactic acidosis has been reported in pregnant women who received the combination of stavudine and didanosine with other antiretroviral agents. It is unclear if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in nonpregnant individuals receiving nucleoside analogues (see **WARNINGS: Lactic Acidosis/Severe Hepatomegaly with Steatosis/Hepatic Failure). The combination of stavudine and didanosine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk.** Health care providers caring for HIV-infected pregnant women receiving stavudine should be alert for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to stavudine and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in lactating rats demonstrated that stavudine is excreted in milk. Although it is not known whether stavudine is excreted in human milk, there exists the potential for adverse effects from stavudine in nursing infants. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving ZERIT.**

Pediatric Use

Use of stavudine in pediatric patients is supported by evidence from adequate and well-controlled studies of stavudine in adults with additional pharmacokinetic and safety data in pediatric patients.

Adverse events that were reported to occur in 105 pediatric patients receiving ZERIT 2 mg/kg/day for a median of 6.4 months in study ACTG 240 were generally similar to those reported in adults.

Stavudine pharmacokinetics have been evaluated in 25 HIV-infected pediatric patients ranging in age from 5 weeks to 15 years and in weight from 2 to 43 kg after IV or oral administration of single doses and twice-daily regimens (see **CLINICAL PHARMACOLOGY,** Table 1).

Geriatric Use

Clinical studies of ZERIT (stavudine) did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently than younger patients. Greater sensitivity of some older individuals to the effects of ZERIT cannot be ruled out.

In a monotherapy Expanded Access Program for patients with advanced HIV infection, peripheral neuropathy or peripheral neuropathic symptoms were observed in 15 of 40 (38%) elderly patients receiving 40 mg twice daily and 8 of 51 (16%) elderly patients receiving 20 mg twice daily. Of the approximately 12,000 patients enrolled in the Expanded Access Program, peripheral neuropathy or peripheral neuropathic symptoms developed in 30% of patients receiving 40 mg twice daily and 25% of patients receiving 20

mg twice daily. Elderly patients should be closely monitored for signs and symptoms of peripheral neuropathy.

ZERIT is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function. Dose adjustment is recommended for patients with renal impairment (see **DOSAGE AND ADMINISTRATION: Dosage Adjustment**).

ADVERSE REACTIONS

Adults

Fatal lactic acidosis has occurred in patients treated with ZERIT in combination with other antiretroviral agents. Patients with suspected lactic acidosis should immediately suspend therapy with ZERIT. Permanent discontinuation of ZERIT should be considered for patients with confirmed lactic acidosis.

ZERIT therapy has rarely been associated with motor weakness, occurring predominantly in the setting of lactic acidosis. If motor weakness develops, ZERIT should be discontinued.

ZERIT (stavudine) therapy has also been associated with peripheral sensory neuropathy, which can be severe, is dose related, and occurs more frequently in patients being treated with neurotoxic drug therapy, including didanosine, in patients with advanced HIV infection, or in patients who have previously experienced peripheral neuropathy.

Patients should be monitored for the development of neuropathy, which is usually manifested by numbness, tingling, or pain in the feet or hands. Stavudine-related peripheral neuropathy may resolve if therapy is withdrawn promptly. In some cases, symptoms may worsen temporarily following discontinuation of therapy. If symptoms resolve completely, patients may tolerate resumption of treatment at one-half the dose (see **DOSAGE AND ADMINISTRATION**). If neuropathy recurs after resumption, permanent discontinuation of ZERIT should be considered.

When ZERIT is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when ZERIT is used alone. Pancreatitis,

peripheral neuropathy, and liver function abnormalities occur more frequently in patients treated with the combination of ZERIT and didanosine, with or without hydroxyurea. Fatal pancreatitis and hepatotoxicity may occur more frequently in patients treated with ZERIT in combination with didanosine and hydroxyurea (see **WARNINGS** and **PRECAUTIONS**).

Selected clinical adverse events that occurred in adult patients receiving ZERIT (stavudine) in a controlled monotherapy study (Study AI455-019) are provided in Table 3.

Table 3: Selected Clinical Adverse Events in Study AI455-019[a] (Monotherapy)

	Percent (%)	
Adverse Events	ZERIT (40 mg twice daily) (n=412)	zidovudine (200 mg 3 times daily) (n=402)
Headache	54	49
Diarrhea	50	44
Peripheral Neurologic Symptoms/Neuropathy	52	39
Rash	40	35
Nausea and Vomiting	39	44

[a] Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.

Pancreatitis was observed in 3 of the 412 adult patients who received ZERIT in a controlled monotherapy study.

Selected clinical adverse events that occurred in antiretroviral naive adult patients receiving ZERIT from two controlled combination studies are provided in Table 4.

Table 4: Selected Clinical Adverse Events in START 1 and START 2[a] Studies (Combination Therapy)

Adverse Events	Percent (%)			
	START 1		**START 2**	
	ZERIT + lamivudine + indinavir (n=100[b])	zidovudine+ lamivudine+ indinavir (n=102)	ZERIT+ didanosine+ indinavir (n= 102[b])	zidovudine+ lamivudine+ indinavir (n=103)
Nausea	43	63	53	67
Diarrhea	34	16	45	39
Headache	25	26	46	37
Rash	18	13	30	18
Vomiting	18	33	30	35
Peripheral Neurologic Symptoms/Neuropathy	8	7	21	10

[a] START 2 compared two triple-combination regimens in 205 treatment-naive patients. Patients received either ZERIT (40 mg twice daily) plus didanosine plus indinavir or zidovudine plus lamivudine plus indinavir.

[b] Duration of stavudine therapy = 48 weeks.

Pancreatitis resulting in death was observed in patients treated with ZERIT (stavudine) plus didanosine, with or without hydroxyurea, in controlled clinical studies and in postmarketing reports.

Selected laboratory abnormalities reported in a controlled monotherapy study (Study AI455-019) are provided in Table 5.

Table 5:	**Selected Adult Laboratory Abnormalities in Study AI455-019[a,b]**	
	Percent (%)	
Parameter	ZERIT (40 mg twice daily) (n=412)	zidovudine (200 mg 3 times daily) (n=402)
AST (SGOT) (>5.0 x ULN)	11	10
ALT (SGPT) (>5.0 x ULN)	13	11
Amylase (≥1.4 x ULN)	14	13

[a] Data presented for patients for whom laboratory evaluations were performed.
[b] Median duration of stavudine therapy = 79 weeks; median duration of zidovudine therapy = 53 weeks.
ULN = upper limit of normal.

Selected laboratory abnormalities reported in two controlled combination studies are provided in Table 6 and Table 7.

Table 6: Selected Laboratory Abnormalities in START 1 and START 2 Studies (Grades 3-4)

Parameter	Percent (%)			
	START 1		**START 2**	
	ZERIT + lamivudine + indinavir (n=100)	Zidovudine+ lamivudine+ indinavir (n=102)	ZERIT+ didanosine + indinavir (n= 102)	zidovudine+ lamivudine+ indinavir (n=103)
Bilirubin (>2.6xULN)	7	6	16	8
SGOT (AST) (>5xULN)	5	2	7	7
SGPT (ALT) (>5xULN)	6	2	8	5
GGT (>5xULN)	2	2	5	2
Lipase (>2xULN)	6	3	5	5
Amylase (>2xULN)	4	<1	8	2

ULN = upper limit of normal.

Table 7: Selected Laboratory Abnormalities in START 1 and START 2 Studies (All Grades)

Parameter	Percent (%)			
	START 1		**START 2**	
	ZERIT+ lamivudine + indinavir (n=100)	zidovudine+ lamivudine+ indinavir (n=102)	ZERIT+ didanosine+ indinavir (n=102)	zidovudine+ lamivudine+ indinavir (n=103)
Total Bilirubin	65	60	68	55
SGOT (AST)	42	20	53	20
SGPT (ALT)	40	20	50	18
GGT	15	8	28	12
Lipase	27	12	26	19
Amylase	21	19	31	17

Observed During Clinical Practice

The following events have been identified during post-approval use of ZERIT (stavudine). Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness, frequency of reporting, causal connection to ZERIT, or a combination of these factors.

Body as a Whole - abdominal pain, allergic reaction, chills/fever, and redistribution/accumulation of body fat (see **PRECAUTIONS: Fat Redistribution**).

Digestive Disorders - anorexia.

Exocrine Gland Disorders – pancreatitis [including fatal cases (see **WARNINGS**)].

Hematologic Disorders - anemia, leukopenia, and thrombocytopenia.

Liver - lactic acidosis and hepatic steatosis (see **WARNINGS**), hepatitis and liver failure.

Musculoskeletal - myalgia.

Nervous System—insomnia, severe motor weakness (most often reported in the setting of lactic acidosis, see **WARNINGS**).

Pediatric Patients

Adverse reactions and serious laboratory abnormalities in pediatric patients were similar in type and frequency to those seen in adult patients.

OVERDOSAGE

Experience with adults treated with 12 to 24 times the recommended daily dosage revealed no acute toxicity. Complications of chronic overdosage include peripheral neuropathy and hepatic toxicity. Stavudine can be removed by hemodialysis; the mean ± SD hemodialysis clearance of stavudine is 120 ± 18 mL/min. Whether stavudine is eliminated by peritoneal dialysis has not been studied.

DOSAGE AND ADMINISTRATION

The interval between doses of ZERIT (stavudine) should be 12 hours. ZERIT may be taken without regard to meals.

Adults: The recommended dose based on body weight is as follows:

40 mg twice daily for patients ≥60 kg.
30 mg twice daily for patients <60 kg.

Pediatrics: The recommended dose for pediatric patients weighing less than 30 kg is 1 mg/kg/dose, given every 12 hours. Pediatric patients weighing 30 kg or greater should receive the recommended adult dosage.

Dosage Adjustment

Patients should be monitored for the development of peripheral neuropathy, which is usually manifested by numbness, tingling, or pain in the feet or hands. These symptoms may be difficult to detect in young children (see **WARNINGS**). If these symptoms develop during treatment, stavudine therapy should be interrupted. Symptoms may resolve if therapy is withdrawn promptly. In some cases, symptoms may worsen temporarily following discontinuation of therapy. If symptoms resolve completely, patients may tolerate resumption of treatment at one-half the recommended dose:

20 mg twice daily for patients ≥60 kg.
15 mg twice daily for patients <60 kg.

If peripheral neuropathy recurs after resumption of ZERIT, permanent discontinuation should be considered.

Renal Impairment

ZERIT may be administered to adult patients with impaired renal function with adjustment in dose as shown in Table 8.

Table 8:	Recommended Dosage Adjustment for Renal Impairment	
Creatinine Clearance (mL/min)	Recommended ZERIT Dose by Patient Weight	
	≥60 kg	<60 kg
>50	40 mg every 12 hours	30 mg every 12 hours
26-50	20 mg every 12 hours	15 mg every 12 hours
10-25	20 mg every 24 hours	15 mg every 24 hours

Since urinary excretion is also a major route of elimination of stavudine in pediatric patients, the clearance of stavudine may be altered in children with renal impairment. Although there are insufficient data to recommend a specific dose adjustment of ZERIT in this patient population, a reduction in the dose and/or an increase in the interval between doses should be considered.

Hemodialysis Patients

The recommended dose is 20 mg every 24 hours (≥60 kg) or 15 mg every 24 hours (<60 kg), administered after the completion of hemodialysis and at the same time of day on non-dialysis days.

Method of Preparation

ZERIT (stavudine) for Oral Solution

Prior to dispensing, the pharmacist must constitute the dry powder with purified water to a concentration of 1 mg stavudine per mL of solution, as follows:

1. Add 202 mL of purified water to the container.
2. Shake container vigorously until the powder dissolves completely. Constitution in this way produces 200 mL (deliverable volume) of 1 mg/mL stavudine solution. The solution may appear slightly hazy.
3. Dispense solution in original container with measuring cup provided. Instruct patient to shake the container vigorously prior to measuring each dose and to store the tightly closed container in a refrigerator, 36° to 46° F (2° to 8° C). Discard any unused portion after 30 days.

HOW SUPPLIED

ZERIT® (stavudine) Capsules are available in the following strengths and configurations of plastic bottles with child-resistant closures:

Table 9:	**Capsule Strength/Configuration**			
Product Strength	Capsule Shell Color	Markings on Capsule (in Black Ink)	Capsules per Bottle	NDC No.
15 mg	Light yellow & dark red	BMS 1964 15	60	0003-1964-01
20 mg	Light brown	BMS 1965 20	60	0003-1965-01
30 mg	Light orange & dark orange	BMS 1966 30	60	0003-1966-01
40 mg	Dark orange	BMS 1967 40	60	0003-1967-01

ZERIT® (stavudine) for Oral Solution is a dye-free, fruit-flavored powder that provides 1 mg of stavudine per mL of solution upon constitution with water. Directions for solution preparation are included on the product label and in the **DOSAGE AND ADMINISTRATION** section of this insert. ZERIT for Oral Solution (NDC No. 0003-1968-01) is available in child-resistant containers that provide 200 mL of solution after constitution with water.

US Patent No.: 4,978,655

Storage

ZERIT Capsules should be stored in tightly closed containers at controlled room temperature, 59° to 86° F (15° to 30° C).

ZERIT for Oral Solution should be protected from excessive moisture and stored in tightly closed containers at controlled room temperature, 59° to 86° F (15° to 30° C). After constitution, store tightly closed containers of ZERIT for Oral Solution in a refrigerator, 36° to 46° F (2° to 8° C). Discard any unused portion after 30 days.

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